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PHARMACOEPIDEMIOLOGY (U HAUG, SECTION EDITOR)

Mixed Bag "Polypharmacy": Methodological Pitfalls and Challenges of This Exposure Definition

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Abstract

Purpose of Review The use of multiple medications is common in older adults but is associated with negative health outcomes. However, polypharmacy is not uniformly defined, and there is scant data on how the variety of definitions and their limitations hinder the development of sound scientific knowledge. The article intends to illustrate the challenges of this exposure definition.

Recent Findings The array of thresholds for defining polypharmacy renders comparisons between results difficult. Few studies take into account the fact that polypharmacy is a changing exposure over time. In addition, although studies tend to recognize the confounding effect of multimorbidity, residual bias remains a concern.

Summary Current studies in polypharmacy often ignore basic epidemiological principles for defining exposure. Future research should integrate time-varying exposure and methods to better control confounding bias. This will help determine the positive/negative impacts of polypharmacy and help establish if polypharmacy conveys information beyond being a marker of health status.

Keywords Pharmacoepidemiology · Polypharmacy · Definition · Exposure · Methodology

Introduction

Polypharmacy has become an important public health issue in recent decades [1]. With the aging of the population, the accumulation of chronic diseases has led to widespread use of multiple therapies in the same individual. Other acute or non-acute conditions such as insomnia, infections, or pain add sporadically or continuously to the burden of pharmacotherapy. Hence, the use of multiple medications has become a standard rather than an exception for many individuals, especially at older ages [2–4].

Although medications bring substantial health benefits, their accumulation raises concerns: large numbers of medications are associated with adverse drug reactions [5], increased risk of drug-drug or drug-disease interactions [6, 7], or the use of potentially inappropriate medications [8]. These concerns are especially relevant for older adults, as age-related metabolic changes make them more prone to medication adverse events. In fact, polypharmacy is widely associated with negative health outcomes, such as hospitalizations [9], falls [10], or frailty [11].

However, there are several impediments to research performed in the context of polypharmacy. One major concern is the limitation of this exposure definition. First, the lack of uniformity in the definition of polypharmacy is well known; literature reviews identified several dozen different definitions in recently published literature [12•, 13•]. Such diversity leads to many challenges, one being the difficulty of comparing and contrasting prevalence and factors associated with polypharmacy. Above and beyond this diversity, exposure definitions rarely correspond to basic epidemiologic

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standards of how exposure should be conceptualized. The complex conditions and circumstances driving the occurrence of polypharmacy accentuate the difficulty of following the basic requirements of exposure definition. To provide some insight into these issues, we retrieved recent manuscripts that addressed the impact of polypharmacy on health outcomes to exemplify the lack of robustness in some definitions and the significant pitfalls and challenges that result.

Methods

We performed a basic literature review looking in PubMed to include articles published in the last 5 years (From January 1st, 2014 to January 7th, 2019). We aimed to include articles that (1) had polypharmacy as a main subject (we thus restricted the search to articles that had polypharmacy in their titles to ensure it was a main exposure); (2) involved adults (as polypharmacy may be conceived differently for younger populations); (3) focused on a health outcome associated with polypharmacy; (4) evaluated polypharmacy as a consequence of treating multiple diseases (that is, we excluded polypharmacy that focused on treating a single condition, for example using multiple medications in the context of an organ transplant).

The articles were scanned for the following information:

(1) Which threshold was chosen for the definition of polypharmacy? Was there any quality element involved in the definition (e.g., use of potentially inappropriate medications)?
(2) Which medications were included in the definition of polypharmacy? Which sources of information were used? Were medications evaluated as a spontaneous exposure or cumulative over a period? Was there any time-varying exposure evaluation?
(3) Did the exposure precede the studied outcome(s)? Was there sufficient time latency before the outcome(s)? Did the authors consider residual effect?
(4) Which comparator was used?

Results

Our literature search, performed on January 7th, 2019, yielded a total of 749 titles, of which 70 fulfilled the criteria and could be retrieved (flow diagram available on demand). Using these recent publications as examples, we explored different issues related to the polypharmacy exposure hereby described.

Polypharmacy: Versatile Definitions with Versatile Comparators

Not surprisingly, our review retrieved many definitions of polypharmacy. Medications were treated as continuous variables in ten (14%) studies, either as the main exposure definition or in combination with additional analyses using other definitions. In six (9%) studies, the authors conducted ROC analysis to decide on the threshold that should be used. Otherwise, we retrieved 23 different definitions of polypharmacy displaying various thresholds and categorizations (Table 1). About a third ($n = 23$) of studies used a cut-off of ≥ 5 medications. The fact that health outcomes have been associated with the use of ≥ 5 medications in older men is one possible explanation for the wide acceptance of this cut-off value [83]. Many authors also used a cut-off of ten medications, often described as excessive polypharmacy or hyperpolypharmacy, since large proportions of older individuals are using more than five medications. However, this terminology may lead to confusion, because polypharmacy is thus either described as the use of five to nine medications (i.e., excluding hyperpolypharmacy) or ≥ 5 medications (i.e., including hyperpolypharmacy). In some instances, from the articles we retrieved, polypharmacy was defined as the use of ≥ 5 medications, but the analyses were actually performed with groups of individuals using five to nine medications [69, 70, 72, 75–77].

The threshold used to define polypharmacy will necessarily influence the comparator or reference category. However, for the same threshold, the reference category may vary between studies. Thus, an odds ratio of 2 for a polypharmacy exposure defined as the use of ten medications or more must be interpreted differently if the respective comparator is the use of 0, 0–4, or 0–9 drugs. Table 1 includes various examples where polypharmacy thresholds were paired with varying reference categories. The choice of a reference category also entails important theoretical considerations. Payne et al., for example, selected the group with one to three medications as the reference rather than the one using no medications because the latter group may not be representative of multimorbid individuals [9].

In addition to these quantitative definitions, polypharmacy may also be viewed as the use of more medications than clinically needed, which constitutes a "qualitative" definition. The fact that polypharmacy is tightly connected with potentially inappropriate medications (the more medications there are, the greater the likelihood of using inappropriate ones), may lead to some confusion between the two phenomena, especially as it is not uncommon to use potentially inappropriate medications as quality indicators in studies focusing on polypharmacy. Qualitative definitions without quantitative elements are, however, rarely used in research [12•]. Since clinical judgement is required to describe this kind of polypharmacy, its application

Table 1 Examples of polypharmacy definitions and respective reference categories used in studies where health outcomes are evaluated ($n = 70$ articles)

Polypharmacy definition	*N* (%)	Reference category	Health outcomes
Continuous count of medications	10 (14%)		• Adverse drug reactions [14] • Adverse drug reactions, falls, frailty, disability, cognitive impairment, mortality [15] • Cardiovascular mortality [16] • Cognitive, physical and emotional function ["triad of impairment"] [17] • Falls, functional decline, institutionalization, rehospitalization, combined endpoints of adverse outcomes (including mortality) [18] • Hospitalization and chemotherapy toxicity [19] • Ischemic and hemorrhagic events [20] • Mobility and cognitive impairment [21] • Mortality [22] • Postoperative readmission and death rate after hip fracture surgery [23]
ROC curve	6 (9%)		• Falls and fractures [24] (people with HIV and substance dependence) • Frailty [25, 26] • Frailty, physical function, Karnofsky performance scale, falls, exhaustion (older cancer patients) [27] • Mobility and cognitive impairment [21] • Overdose [28]
≥ 5 medications	23 (33%)	0–1 ($n = 1$) < 5 ($n = 21$) < 5 + non-frail ($n = 1$)	• Adverse drug events/reactions [14*, 29] (*no comparators, all patients with polypharmacy) • Adverse events and complications, duration of hospitalization, noncancer health event [30] • Cardiovascular mortality [16] • Chronic kidney disease [31] • Cognitive function [32] • Cognitive, physical and emotional function ["triad of impairment"] [17] • Disability [33] • Falls, emergency room visits, and hospitalizations [34, 35] • Falls, functional disability, healthcare utilization, potential drug-drug interactions, potentially inappropriate medications, and quality of life [36] • Fatigue, depression, cognition [37] • Hospitalization [38] • Hospitalization, institutionalization, and mortality [39•] • Major bleeding [40] • Mobility and cognitive impairment [21] (following ROC curve analyses) • Mortality [41–43] • Mortality, incident disability, hospitalization, emergency room visits [44] • Mortality, response rate, and toxicity (chemotherapy) [45] • Road accident deaths [46] • Sarcopenia [47]
≥ 6 medications	2 (3%)	< 6	• Frailty [26] (following ROC curve analyses) • Heart rate [48] • Quality of life [49] (+sensitivity analyses with ≥ 4 and ≥ 5)
≥ 9 medications	2 (3%)	0–8	• Hospitalizations [50] • Discharge destination [51]
0, 1–2, 3–5, 6–9, 10+	1 (1%)	0	• Acute pancreatitis [52]
0, 1–3, 4–6, 7–9, 10+	2 (3%)	1–3 ($n = 1$)	• Hospitalizations [9]

Table 1 (continued)

Polypharmacy definition	*N* (%)	Reference category	Health outcomes
		0 ($n = 1$)	• Non-cardiovascular hospitalizations [53]
0, 1–5, ≥ 6 (polypharmacy: ≥ 6)	1 (1%)	0	• Mortality [54]
0, 1–5, 6–10, 11+	1	0	• Mortality (other: toxicity, discontinuation of chemotherapy) [55]
0–1, 2–3, 4+	1	0–1	• Mortality, complete remission, intensive care unit stay, length of stay [56]
0–3, 4–5, 6–9, 10+	1 (1%)	4	• Hospitalizations, mortality [57]
0–3, 4–6, 7+	2 (3%)	0–3	• Emergency department visits, any and unplanned hospital admissions, mortality [58] • Frailty [59]
0–3, 4–9, 10+	1 (1%)	0–3	• Hospitalizations and chemotherapy toxicity [19]
0–5, 6–9, 10+ (non-polypharmacy; polypharmacy; excessive polypharmacy)	2	0–5	• Hospitalizations [60] • (*Polypharmacy defined in categories, but analyses performed with continuous count of medications for adverse drug reactions, falls, frailty, disability, cognitive impairment, mortality* [15]*)*
1–4, 5–8, 9+ (no polypharmacy; moderate poly-pharmacy; marked polypharmacy)	1 (1%)	1–4	• Bleeding, thromboembolic events (PE, thrombosis, systemic embolism, stroke, MI), hospitalization, and all-cause mortality [61]
1–4, 4–9, 10+[a]	1	1–4 and 4–9	• Quality of life [62]
2–4 (minor polypharmacy), 5+ (major polypharmacy)	1	2–4	• Quality of life [63]
> 2 and ≥ 5 non-anti-HIV	1	0–1/> 5	• Hospitalizations and mortality [64]
From ≥ 4 to ≥ 10	1	Varied according to definition used	• Falls [65]
≥ 4 categories of fall related medications	1	0 category of fall related medications	• Fall-related fractures [66]
5–7 (moderate polypharmacy), 8+ (severe polypharmacy)	1	0–4	• Cardiovascular mortality, stroke [16]
5–8 (polypharmacy), 9+ (excessive polypharmacy)	1	0–4	• Physical and cognitive capabilities [67]
5–9 (polypharmacy), 10+ (excessive polypharmacy/hyperpolypharmacy)	9 (13%)	< 5 ($n = 8$) 1–4 ($n = 1$) < 1 ($n = 3$)	• Adverse drug events [68] • Dementia [69][b] • Frailty [70[b], 71] • Hip fracture [72][b] • Hospitalization, fracture-specific admission to hospital, death [73] • In-hospital: fall; delirium; ADL function decline; cognitive function decline; mortality. Discharge to a higher level of care // Combination of all those adverse outcomes [74] • Ischemic and hemorrhagic events [20] • Mortality [75, 76][b] • Parkinson [77][b] • Physical and cognitive function [78]
≥ 5 and ≥ 8	1	< 5 and < 8	• Gait performance [79]
≥ 5 (polypharmacy) and ≥ 10 (hyperpolypharmacy)	3 (4%)	0–4	• Delirium [80] • Long hospital stay, institutionalization, readmission and death [81] • Mortality [82]

Some articles presented more than one definition

[a] The categories are not mutually exclusive but were defined as such in the article

[b] Polypharmacy defined as ≥ 5 medications, but analyses performed with a group using 5–9 medications. Conclusions made with polypharmacy as the use of ≥ 5 medications

in research and population health may be limited because it often necessitates a holistic evaluation of the individual, including clinical data, complete medical history, and patients' motivations, which are rarely fully collected. Moreover, this approach is more sensitive to subjective interpretation by health practitioners, limiting the standardization required for rigorous research.

Polypharmacy: an Exposure Definition that Eludes Foundations of Exposure

Following epidemiological principles, exposure should be defined in terms of dose, duration, and temporal relationship with the occurrence of the outcome under study [84]. Figure 1 illustrates how these concepts could be integrated into the definition of polypharmacy. Obviously, the type of study and the studied outcome will influence the definition that will be chosen, but some principles should be followed.

Conceptualization of Exposure Polypharmacy is neither permanent, like genetic constitution or sex, nor instantaneous, like vaccination or accidents. Exposure to polypharmacy could be constant and continuous over a period, but will often be variable, with some individuals fluctuating between exposed and non-exposed over time [85•, 86, 87]. Seasonal variation, for example, is likely to occur as the use of medications increases during winter time, although such seasonal polypharmacy does not seem to have been studied so far. Changing exposure

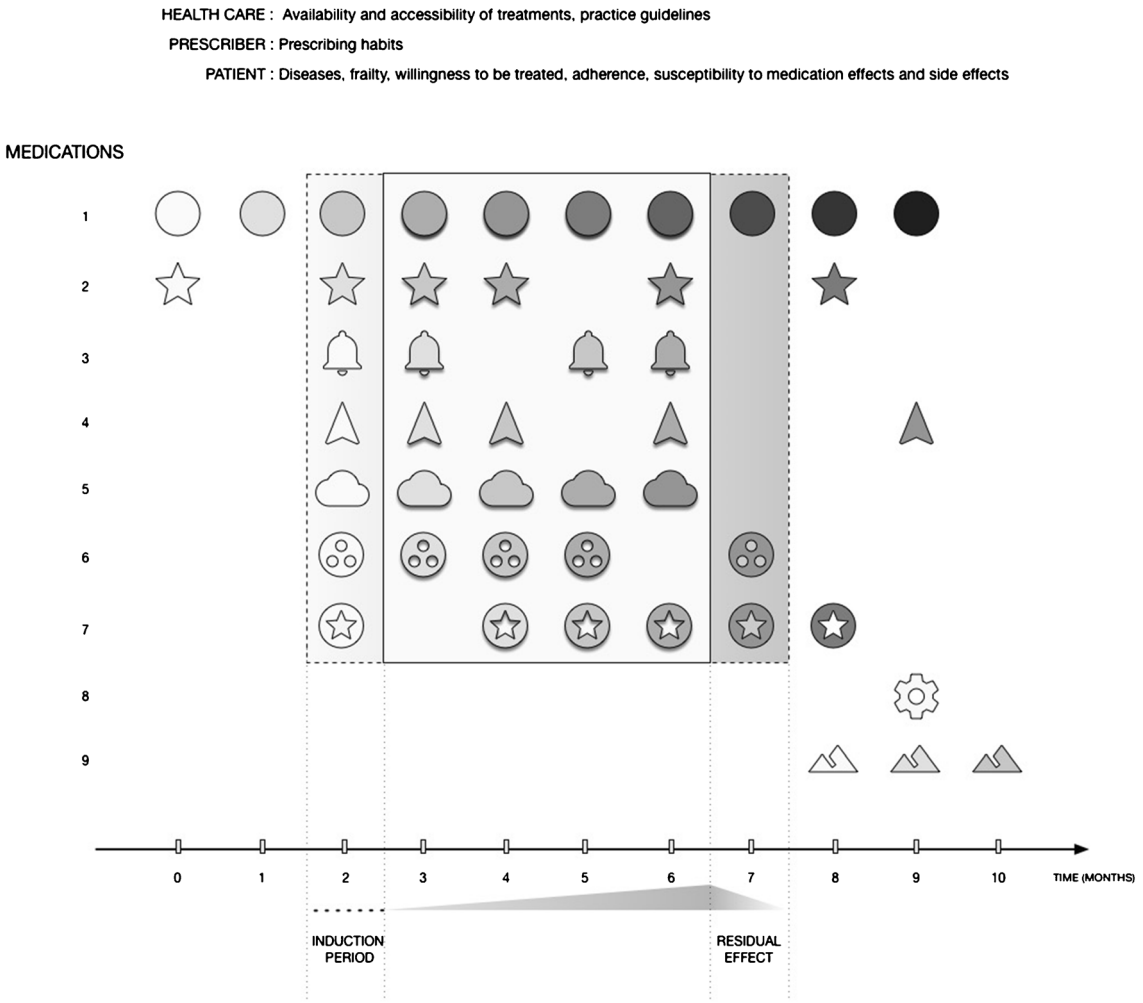

Fig. 1 The figure shows medication use by an individual over time and how exposure to polypharmacy can be defined. The square represents the window of exposure where the individual is considered exposed to polypharmacy (use of five medications simultaneously). Dotted lines are the periods of induction (a period of time where outcome would not be considered associated with the exposure) and the residual effect (the period during which the effect of exposure may be felt even if the individual is no longer exposed to polypharmacy). The increasing arrow at the bottom of the graph indicates that cumulative exposure to polypharmacy increases over time and then declines on stopping. The cumulative effect of each drug is represented by the color gradient that increases over time. Note that the individual would never be considered exposed to polypharmacy if the definition involved the use of five (regular) medications used consecutively for at least 3 months. At the top of the chart are the different aspects that influence drug use, and therefore polypharmacy, at the patient/care giver, prescriber, and health system levels

would call for integrating time-dependent exposure definitions, so that changes in exposure levels during follow-up are taken into account. However, spontaneous count of medications, that is the number of medications the person is using on a particular day, such as the day the person enters a cohort or is hospitalized, was the most frequent method (77%) used to define polypharmacy in the 70 articles we retrieved. While spontaneous count often relate to the simultaneous use of medications, there are obvious drawbacks to considering this exposure as definitive. Other ways of counting medications are also encountered, but still do not portray evolution over time. First, one can evaluate the number of medications used over a period of time, no matter how long or often the medication is used (cumulative count). Second, one can consider only those medications that are used regularly over a period of time (regular use). Yet, when using claims data, one can only estimate treatment periods based on dates of dispensation and rely on assumptions in situations where treatments are added (i.e., decide if it is a switch or a combination of treatments). In practice, the choice of counting method has profound effects on whether an individual will be considered exposed to polypharmacy or not [88, 89•]. In Fig. 1, for example, using a threshold of five medications, an individual would be considered exposed to polypharmacy at month 2 under both spontaneous and cumulative count definitions. However, the same individual would not meet the definition of regular concomitant use of five medications, if regular use entailed using medications for at least 3 consecutive months. It is difficult to evaluate what impact each different definition has on outcomes and what counting method would allow more correct evaluation. There is a need for research to evaluate these elements.

Temporal Relationship with the Event In theory, when the exposure is not instantaneous, it must be maintained for a period deemed sufficient to produce an impact on health. During this exposure-qualifying period, the person should be considered non-exposed. This induction period depends on outcome in question. The relevant exposure window for alcohol consumption is not the same if the outcome is an accident or cirrhosis. However, in studies on polypharmacy, this temporal relationship is rarely highlighted; the time required to determine the effect of polypharmacy on health events is usually not mentioned. In fact, it can be complicated to separate the short-term and cumulative effects of polypharmacy. Drug interactions or side effects may have immediate consequences, such as bleeding or falls, thereby increasing, among other things, the risks of hospitalization. But other effects, such as frailty or altered cognition, may require a much longer induction period. Few authors evaluate such elements. Nonetheless, all temporal relations must respect one fundamental rule: the exposure must precede the event. In one study we retrieved, this rule was not explicit, and outcomes could in fact happen before the actual polypharmacy exposure [28].

Doses and Dose-Duration Combination What "polypharmacy dose" an individual receives is an important question. This could be conceptualized as a maximum dose, i.e., the maximum number of medications received during a period, the average dose over a period, or the cumulative dose over a period. Among the studies we retrieved, three calculated a weighted average number of daily medications over a period [69, 72, 77]. In other domains, exposure definitions combine dose and length of exposure: electromagnetic fields or smoking for example, use composite measures assuming that a high dose of short duration has the same effect as a low dose of long duration. Assessing how this composite measure could be applicable to polypharmacy might prove relevant for studying health outcomes.

Polypharmacy: an Exposure of Exposures

Defining polypharmacy adequately represents a significant challenge because polypharmacy is itself an exposure to several exposures. Each of the included medications has its own risks and benefits, its own drug-drug, and drug-disease interactions. In fact, considering the myriad combinations that are possible with the numerous medications available on the market, polypharmacy is really polypharmacies.

For each drug, the characteristics of exposure as described in the previous section may vary. Additionally, the factors that influence the use of each medication are legion. Some stem from individuals themselves, such as the type and severity of their chronic diseases, the more or less complex treatments they require, treatment adherence, individual medication sensitivity or susceptibility to side effects, and the influence of their caregivers. Prescribers may exert an influence by treating more aggressively or preferring certain types of treatments over others. The health care system may influence polypharmacy through varying accessibility or availability of treatments and the evolution of practice guidelines. Decentralized health system may also lead to polypharmacy when different physicians prescribe independently from each other, without a unifying vision of the patient's treatment goals.

Hence, the diversity of treatments, the individual characteristics of patients, and the particularities of prescribers invariably lead to a diversity of polypharmacies. The question at stake is therefore: is exposure to one set of medications similar to the exposure to a different set of medications? Does the effect of polypharmacy depend on the nature and characteristics of each medication included in a particular list? For example, should a set of five medications composed of acetaminophen, calcium, vitamin D, levothyroxine and iron supplement be considered on the same level as the use of metformin, ACE inhibitor, aspirin, thiazide diuretic, and statin, even after adjustment for comorbidities? Again, very seldom are these questions raised in polypharmacy research.

Indeed, polypharmacy is not necessarily about prescription medications alone. To examine a complete portrait of medication use, non-prescribed medications could be introduced. Few studies include over the counter (OTC) or natural products, because the information is often not available, especially for those studies using administrative databases. Some OTC products may have real potential side effects (e.g., ibuprofen) and specific interactions (e.g., St. John's wort), while for others, such as homeopathy, the effect is likely to be minimal or even nil.

Appropriate and Inappropriate Polypharmacies

There is substantial evidence that individual medications bring benefits for many chronic diseases. Because polypharmacy is almost necessary when several chronic diseases accumulate [90], some combinations of medications should lead to health benefits. Nonetheless, appropriate polypharmacy is rarely studied in observational research. Several researchers and organizations have called for differentiating appropriate and inappropriate polypharmacy [91, 92]. Burt et al. have developed a set of 12 implicit criteria that could help identify appropriate polypharmacy [93]. Yet, as exposed by the authors, the operationalization of those indicators and their integration into computerized systems might limit their applicability. There is also a need to evaluate their impact on health outcomes. Hence, to date, there are still few evidence-based guidelines to help distinguish appropriate and inappropriate polypharmacy. This indeed proves difficult in research, as appropriateness is highly related to patient's estimated risks and willingness to be treated. For example, a polypharmacy composed of five cardioprotective drugs—aspirin, ACE inhibitor, diuretic, statin, beta-blocker—may be appropriate for a 65-year-old who has had a heart attack but may appear inappropriate in the same individual at 90 years old with a limited life expectancy.

Polypharmacy has consistently been associated with negative outcomes—which would appear to be inappropriate polypharmacy. However, there must also be appropriate polypharmacy associated with positive consequences, and this should be better described in the scientific literature. Again, this demonstration will entail significant challenges. The previous example illustrates one such challenge: the benefit/risk ratio of polypharmacy may reverse over time. Indeed, considering multimorbid individuals are living longer, the circumstances under which a patient is exposed to polypharmacy may change drastically over the years. A polypharmacy that first brought overall benefits may over time be associated with negative outcomes, as the person ages and becomes more vulnerable to medication side effects, and less likely to benefit from long-term protective therapy [94].

Polypharmacy as an Evolving Condition

Exposure to polypharmacy is usually not a stable and instant exposure. In fact, since polypharmacy is the accumulation of medications, which should, at least partly, be the consequence of chronic diseases, Kadam et al. suggest that polypharmacy could be defined with a primary disease to which comorbidities are subsequently attached [95]. Clusters of diseases have indeed been identified in polypharmacy [96]. Nevertheless, there may be practical limitations to the approach Kadam et al. propose. First, it requires long-term follow-up to clearly define the sequence of diseases, which is not always easy to accomplish. Second, it is often very difficult to determine the chronology of events. For example, a newly detected renal failure may be the consequence of untreated hypertension; treatment of renal failure and high blood pressure may start at the same time they are diagnosed, and the chronology will not be defined. This situation could also include a diagnosis of diabetes—what would then be considered the main or primary disease? Finally, it does not provide specific places for prophylactic treatments, which can contribute to polypharmacy. While the idea is interesting from a theoretical standpoint, it has yet to prove its feasibility in real clinical situations.

Considering these elements, it may be difficult to study incident cases of polypharmacy instead of prevalent cases—for most individuals, drug accumulation occurs over a period of time rather than abruptly. In our review, only one study [39•] investigated new cases of polypharmacy. Obviously, the analysis of prevalent cases of polypharmacy carries methodological limitations, one being the issue of survival bias: only those who have survived long enough to have their medications added up will be exposed to polypharmacy. Indeed, mortality is a competitive risk that poses significant limitation for studying outcomes of polypharmacy, as polypharmacy is most often a cumulative exposure. In fact, there is a need to study incident polypharmacy and answer questions as to whether polypharmacy is a transient or definitive exposure; at what speed polypharmacy builds up; what are the circumstances driving the occurrence of polypharmacy; and which populations are the most at risk of becoming exposed to polypharmacy.

Polypharmacy: a Marker of Health Status or a Risk Factor of Its Own?

Considering the shortcomings related to how polypharmacy exposure is defined in studies, it appears that most studies portray polypharmacy as a proxy of health conditions rather than as an exposure in itself. In fact, one might ask whether polypharmacy is a risk factor of its own or simply a marker of health status [97]. In other words, is polypharmacy responsible for adverse events, or it is only an intermediary path between comorbidities and health events [98••]? Dealing with

confounding is a daunting task, since multimorbidity and frailty are so intimately linked to polypharmacy.

In addition to the exposure, one challenge of studying polypharmacy lies on the fact that the populations exposed to polypharmacy are very heterogeneous. Most of the time, these are older adults with very different physiological characteristics that can affect the pharmacodynamics and pharmacokinetics of medications, and thus make them more vulnerable to the negative effects of medications and of polypharmacy. They are also recruited in different settings (community, nursing homes, hospitals) which are, among other things, markers of their frailty. Contrasting and interpreting the impact of polypharmacy between different studies also implies dealing with these layers of additional complexity.

Polypharmacy and Outcomes: Are the Most Relevant Outcomes Being Studied?

Choices of exposure definitions are intimately tied to the studied outcomes. Outcomes are also linked to the perspective taken (patient, healthcare system, etc); this may in part influence the definition used. Globally, there is a need to evaluate if studied outcomes are relevant for target populations. Studying polypharmacy in the oldest old, for example, may call for the evaluation of these patients' quality of life more than mortality; similarly, the health care system may be interested in the cost-benefit ratio of using medications in these individuals.

Is It Possible/Useful to Study Polypharmacy and Its Consequences with So Many Challenges?

Does the foregoing challenges mean that there is no need to study polypharmacy or that existing research is not useful? Neither is the case. Polypharmacy remains a condition that affects and will affect a large number of individuals and is the most important factor for receiving potentially inappropriate medications. Each medication carries its own potential risk of adverse events, let alone many medications. Research therefore needs to evaluate the epidemiology and impacts of polypharmacy to assess those risks. Conversely, it is paramount to focus on the positive impacts of polypharmacy, which have been neglected in observational studies. In fact, research in polypharmacy reinforces the necessity of regularly reviewing medication to ensure its relevance. There is a need to evaluate under which circumstances a polypharmacy is associated with positive outcomes and under which it is not, as the risk/benefit ratio of polypharmacy evolves with time and circumstances. In terms of public health, knowing which proportion of the population is exposed to polypharmacy associated with positive or negative outcomes provides useful information, for example to forecast use of health services.

The fact that many studies conclude that polypharmacy is a marker of poor prognosis can be very useful when assessing an individual. If the conditions and diseases of an individual are unknown, for example, it would be helpful to know that this individual is at risk of adverse events because they are exposed to polypharmacy. Polypharmacy can thus be a marker of vulnerability easy to calculate and interpret. In fact, the wide variety of definitions of polypharmacy in research appear to be an advantage at this point: polypharmacy is usually overly associated with adverse health outcomes no matter how polypharmacy is calculated and no matter what types of medications are included.

Conclusion

Research in polypharmacy faces several challenges owing to the complexity of this exposure definition. However, following some basic epidemiological rules—as to timing of the exposure, the dose received, and the duration of exposure, among others—would help understand current issues surrounding polypharmacy. To fully highlight the risks and benefits of polypharmacy, research will need to delve into at least two aspects. On the one hand, it is imperative to demonstrate what risk or benefit is intrinsic to polypharmacy—that is to the *combination* of medications rather than to the effects of individual medications. In fact, if the risk is increased (or decreased) regardless of the type of medications included in the polypharmacies, it would be clear that the iatrogenic risk observed is inherent to the conjunction of the medications and not to their own individual effects. On the other hand, it is necessary to highlight the role of polypharmacy beyond the basic risk of multimorbidity or conditions driving medication use (indication bias). These elements are likely necessary for significant changes to be seen among practitioners. Health professionals are torn between clinical practice guidelines that promote the use of multiple drugs in multimorbidity conditions and the idea that polypharmacy can truly be a risk factor for adverse health outcomes. If the risks of polypharmacy are clearly demonstrated, independently from the effects of multimorbidity, then it will be easier for them to restrict the number of medications they prescribe to treat multimorbid individuals as they would be able to support their clinical practice with evidence-based data.

Because studies of polypharmacy are almost always observational, it is indisputable that residual confounding will remain an issue when studying polypharmacy and its impacts: the reasons justifying prescription of each and every medication or combination go far beyond their indications. In addition, changes in practice, variations in the characteristics of treated patients, and modifications of available therapies will lead to frequent changes in the use of medications. It will therefore be necessary to be aware of these variations and take them into consideration when studying polypharmacy over time. Polypharmacy will by default take different faces over

time, but more rigor will prevent it from being a constant mixed bag.

Compliance with Ethical Standards

Conflict of Interest Caroline Sirois reports grants from the *Fonds de recherche du Québec-Santé* and from the *Centre de recherche sur les soins et les services de première ligne de l'Université Laval*. Marie-Eve Gagnon receives a scholarship from the *Fonds de recherche du Québec-Santé*. Marc Simard, Emmanuelle Gosselin, Barbara Roux, and Marie-Laure Laroche declare no conflict of interest.

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- • Of importance
- •• Of major importance

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